Remarks

With respect to the claims, Applicants have amended independent claim 1. The Examiner has withdrawn claims 2-8, 16-19, and 25. New Claim 26 has been added which is the same as Claim 1 except that position 230 is absent. Should the Examiner find amended claim 1 to be allowable, applicants request reconsideration to rejoin method claims 16-19. Should the Examiner reconsider rejoining method claims 16-19, Applicants respectfully request that method claims 16-19 be amended to include new claim 26 as a heterologous fusion protein contemplated for the method claims.

Support for the amendments can be found throughout the specification, but especially on page 6, lines 5 to 8, page 6, lines 8 to 14, page 7, lines 8 to 13, page 7, lines 15 to 25, page 8, lines 26 to 28, page 9, lines 2, 3 and 11, to page 13, lines 13 to 15, and Examples 1 to 7.

REJECTION UNDER 35 U.S.C. § 102

The Examiner rejected Claim 1 under 35 U.S.C. §102(a) and (e) as being anticipated by Glaesner et al. (WO 02/46227). Applicants have amended claim 1 such that it is limited to a specific heterologous fusion protein comprising a GLP-1 analog fused via a linker to a Fc portion of an immunoglobulin. Thus this rejection is now moot.

Should the Examiner consider an obviousness rejection, Applicants make the following comments.

Applicants identified a strong epitope located at the junction of the C terminus of the GLP-1 analog portion and the beginning of the linker. The sequence of this epitope is Trp-Leu-Val-Lys-Gly-Arg-Gly-Gly-Gly (SEQ ID NO:11) which interacts with DRB 1 *0801. (See page 6, lines 5-8). Several proposed sequences in the C-terminus of the GLP-1 analog eliminate this epitope, one of which is Trp-Leu-Val-Lys-Gly-Gly-Gly (SEQ ID NO:12) (See page 6, lines 8-14).

In addition, the Fc portion which is derived from human IgG4, comprises additional substitutions compared to the wild-type human sequence. IgG4 was specifically chosen because of its reduced ability to bind to the Fc receptor FcγR and complement factors compared to other IgG sub-types. IgG4, however, has been shown to deplete target cells in humans. However, as Applicants have pointed out because the heterologous fusion proteins of the present invention target beta cells in the pancreas to induce insulin expression, using an IgG4 derived region in an Fc fusion protein could initiate an immune response against the

pancreateic beta cell through interaction of the fusion protein with the GLP-I receptor present on pancreatic beta cells. (Page 7, lines 8-13). Therefore, Applicants have made specific substitutions that in the IgG4 that minimize or eliminate effector function. The IgG4 Fc portion of the fusion protein contains two substitutions, alanine for phenylalanine at position 17 of SEQ ID NO:7 and alanine for leucine at position 18 of SEQ ID NO:7.

In addition, the IgG4 Fc portion of the heterologous fusion protein contains a substitution, proline for serine at position 11 in SEQ ID NO:7, that stabilizes heavy chain dimmer formnation and prevents the formation of half-IgG4 Fc chains.

Finally, Applicants have optimized function and stability while minimizing potential immunogenicity of the heterologous fusion protein by adding a specific peptide linker, SEQ ID NO. 8 that links the N-terminus of the GLP-1 analog portion to the C-terminus of the Fc immunoglobulin portion.

Thus, the substitution at position 36 in the context of the GLP-1 analog with specific changes at 8 and 22 fused via a specific linker to an IgG4 with two specific substitutions at positions 16 and 17 to reduce effector function wherein the entire fusion protein is designed to have a long plasma half-life and reduces the risk that the fusion protein will induce a neutralizing immune response after repeated and prolonged administration in humans is novel and inventive.

Double Patenting

Applicants note that the Examiner has provisionally rejected Claim 1 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 1 of copending Application No. 10558862. The conflicting application is commonly owned with this application. Applicants will consider filing a terminal disclaimer once claims are in allowable form for both cases.

SUMMARY AND CONCLUSION

Applicants respectfully assert that the application is now in condition for allowance. The specific GLP-1 fusion protein as claimed is novel and inventive. If, for any reason, the Examiner feels that a telephone conversation would be helpful in expediting the prosecution of this case, the Examiner is urged to call me.

Respectfully submitted,

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